The Methionine Adenosyltransferase Subunit MATIIβ Spatially Controls S-adenosyl Methionine Synthesis and Histone Methylations.

（書式１８）

学　位　論　文　要　約
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博士論文題目 Title of dissertation

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メチオニンアデノシルトランスフェラーゼサブユニット MATIIß による S-adenosyl Methionine 合成とヒストンメチル化の空間的制御

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Introduction: Methionine adenosyltransferase II (MATII) catalyzes the synthesis of SAM (S-adenosyl methionine), the major biological methyl donor, and has two subunits; catalytic α and regulatory β subunits. Historically, MATII was thought to locate and catalyze the SAM synthesis in cytosol compartment. However, recent studies revealed that MATIIα and MATIIβ are both present in not only the cytoplasm but also the nucleus of various cell lines. MATIIα was shown to recruit to genes by transcription factors Bach1 and MafK, interacts with histone methyltransferases and promotes histone methylation. MATIIβ interacts with histone deacetylase SIRT1. However, it is unclear whether the presence of MATIIα and/or MATIIβ in the nuclear region is important for histone methylation or gene expression beyond target genes of Bach1 and MafK. Recent unpublished findings suggested that MATIIβ promotes MATIIα nuclear localization. Hence it raises the idea to explore the function of MATII complex within the nucleus through MATIIβ.

Methods: Combining MATIIβ knockdown and methionine restriction, I investigated on the biological meaning of nuclear MATIIα-MATIIβ on histone methylation and gene expression both in normal and low limited SAM conditions. Local regulation of MATIIβ on histone methylation was examined by ChIP-qPCR. I also carried out Mass Spectrometry to explore MATIIβ protein network.

Achivements: I confirmed that MATIIβ is required for nuclear accumulation of MATIIα and discovered that MATIIβ is critical to maintaining of histone methylation and proper genes expression, specially under methionine restriction. MATIIβ is also required for HP1α expression, independently with intracellular SAM levels. HP1α repression upon MATIIβ knockdown might explain for significant H3K27me3 upregulation. MATIIβ knockdown significantly impaired cell movement through repressing mobility-related of genes through histone methylations alteration. Exploring MATIIβ protein network revealed its tight connection to machineries for chromatin remodeling, nuclear membrane and RNA processing proteins. MATIIβ appears to be a crucial epigenetic regulator for gene responses.

Conclusion: MATIIβ is essential for proper regulation of chromatin architecture and gene expression. Combining all these findings, I put MATIIβ or nuclear MATII complex in the crossroad between epigenetic regulation and metabolism. Further investigations with comprehensive approaches will help uncover the mechanism how MATIIβ regulates specific histone methylation and genes regions.